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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,009	07/08/2003	Stanley T. Crooke	ISIS-5138	1016

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/616,009	CROOKE ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,29-37 and 39-74* is/are pending in the application.

4a) Of the above claim(s) *45-48 and 51-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,29-37,39-44,49 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 12/7/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 8/7/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 12/7/2006, claims 1, 29-37, and 39-74 are pending in the application. Claims 45-48 and 51-74 remain withdrawn pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The Examiner notes that claims 33 and 37 were not specifically identified by Applicant as reading on the elected species (see Applicant's response filed 6/29/05, page 14). To the extent that certain embodiments of these claims have been examined, claims 33 and 37 are considered to include elected subject matter.

As noted by Applicants, claim 38 has been canceled; its inclusion in the rejections of record was inadvertent.

Claims 1, 29-37, 39-44, 49, and 50 are currently under examination.

This application contains claims that are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 29-32, 49, and 50 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6 of U.S. Patent No. 6,617,442. Although the conflicting claims are not identical, they are not patentably distinct from each other because Patent No. 6,617,442 discloses a chemically modified, mixed sequence oligonucleotide, having first and further portions, that is embraced by the genus now claimed in the instant application. Accordingly, the species of Patent No. 6,617,442 anticipates the genus of mixed sequence oligonucleotides now claimed in Claims 1, 29-32, 49, and 50.

Applicants' response filed 12/7/06 is noted. Applicants state that in the event that claims 1, 29-32, 49 and 50 are otherwise found to be in condition for allowance in their current form, applicants will file a terminal disclaimer.

The instant rejection is maintained until such time.

Claim Rejections - 35 USC § 112, second paragraph—withdrawn

The rejection of Claims 37 and 39-44 as being indefinite for lack of antecedent basis is withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 102—maintained

Claims 1, 29–32, 34–37, 39–44, 49, and 50 remain rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550).

Response to Arguments

Applicants argue that Agrawal does not teach an embodiment that falls within the scope of the present claimed invention. In particular, Applicants argue that Agrawal does not teach a mixed sequence oligonucleotide wherein, in part, said first portion comprises nucleotides that support cleavage of a complementary target RNA by human RNase H1 polypeptide and wherein said first portion comprises at least 6 contiguous nucleotides and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide. Applicants state that the Agrawal reference does not teach any compound that falls within the scope of the present claimed invention. Applicants contend that Compound D of Fig. 5 in Agrawal does not have a first sequence portion that is at least 6 contiguous nucleotides, and assert that the examiner has not correctly interpreted the nucleotide positioning in compound D in Fig. 5 of Agrawal. The examiner asserted that the

final T in the loop, which is complementary to the first 5' G of the gag RNA, is 8 nucleotides from the 3' end. Applicants argue that this nucleotide is 9 nucleotides from the 3' end.

Applicants go on to argue that none of the compounds described in Figure 5 or elsewhere in the Agrawal reference have a first portion nucleotide sequence that supports cleavage by RNase H and that is at least 6 contiguous nucleotides positioned 8 to 12 nucleotides from the 3' end of the oligonucleotide. Therefore, Applicants state, the Agrawal reference does not anticipate the present claimed invention.

Applicant's arguments (page 14 of 17) filed 12/7/06 have been fully considered but they are not persuasive.

The Examiner respectfully disagrees with Applicants' characterization of Agrawal et al.

In the first, the disclosure of Agrawal et al. is not limited to Compound D, or even to Fig. 5.

In the second, Agrawal et al. teaches each of the limitations of the instant claims. Agrawal teaches a mixed sequence antisense oligonucleotide comprising "first" and "further" portions, as follows. As explained in the previous Action, Agrawal et al. disclose self-stabilized, hairpin antisense oligonucleotides comprising a target hybridizing region and a self complementary region that form a totally or partially double stranded structure. Fig. 5 sets forth exemplary embodiments. The "target hybridizing region" represents the instantly recited "first portion"; the "self complementary region," the "further portion." As shown schematically in Fig. 6, upon exposure to a target mRNA, the target hybridizing region anneals to the complementary sequence in the target, while the self-complementary region remains unbound. Thus, one of skill would immediately recognize from this drawing and from the written description throughout the

Agrawal et al. reference, that the self-complementary region (i.e., the further portion) cannot support RNase H1 cleavage because it cannot hybridize to the target, while the target hybridizing region (i.e., the first portion) can support RNase H1 cleavage because it is complementary to the target.

Going on, Applicants attention is directed to Fig. 6—again, a non-limiting, exemplary embodiment—which shows Compound B of Fig. 5. Following the first arrow, Applicants will note that the first portion—the target hybridizing region, comprises "at least 6 contiguous nucleotides," and that at least one of said 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end—to be specific, the final most 3' nucleotide of the first portion is 9 nucleotides from the 3' end, using Applicants' numbering system.

Applicants' assessment of Compound D is confusing. Applicants appear to argue that because the "T" is 9 nucleotides from the 3' end it is outside the scope of the invention. Claim 1, however, requires only that at least one (not all) nucleotide of the first portion is 8-12 nucleotides from the 3' end. Compound D meets this limitation (compare to Compound B and see Fig. 6), even if the "T" is 9 nucleotides from the end.

Nevertheless, Agrawal et al. is not limited to compound D. Agrawal et al. teaches that a wide variety of self-stabilized hairpins are possible within the scope of their invention. The disclosure covers a complete spectrum of possibilities, ranging from fully duplexed hairpins to partial hairpins. According to Agrawal et al., the guiding principle is that the self-stabilized hairpins be designed so as be thermodynamically less stable than the target-bound complexes, so as to favor mRNA binding and target cleavage over hairpin formation. At page 9, for example, Agrawal et al. state, for example, that "This disruption and replacement of base-pairing takes

place because the intermolecular base-paired structure formed by the hybrid between the target nucleic acid sequence and the target hybridizing region is more thermodynamically stable than the intra-molecular base paired structure formed by the self-complementary oligonucleotide. This phenomenon is illustrated in Figure 3 and discussed in greater detail in Example 4." Accordingly, one of skill in the art would immediately recognize from the disclosure of Agrawal et al. that a wide range of possible self-stabilized structures, comprising target hybridizing regions from about 8 to about 50 nucleotides (page 9 bridging to 10), and wherein there are about 4 or about 10 intramolecular base-pairs formed in the self-stabilized oligonucleotide (page 15).

As previously stated, Agrawal et al. teach that the target hybridizing and a self complementary regions of the oligonucleotide can be composed of ribonucleotides, deoxyribonucleotides, or both (pages 8–16, for example). It is expressly stated at page 16 that the ability to activate RNase H is not important for the self-complementary region, so nucleotides having artificial linkages that do not activate RNase H can be used in this region without diminishing the effectiveness of the oligonucleotide. Thus, in addition to phosphodiester and phosphorothioate or phosphorodithioate linkages, this region may also or alternatively contain phosphoramidate (including N-substituted phosphoramidates).

Additionally, it is taught that the oligonucleotide may include modified nucleic acid bases and/or sugars as well as molecules having added substituents, such as diamines, cholesteryl, or other lipophilic groups (pg. 8). Agrawal et al. clearly teach that the self-stabilized oligonucleotide may be rendered hyperstabilized by incorporating one or more 2'-modifications, known in the art, into the oligonucleotide. Preferred modifications include 2'-O-Me ribonucleotides in the self-complementary region. For example, the target hybridizing region

may contain ribonucleotides or 2'-O-Me-ribonucleotides and the self-complementary region may contain DNA" (page 16). Thus, the Agrawal et al. invention clearly embraces several different combinations of internucleoside and 2'-sugar modifications in the self-stabilized oligonucleotides, and a number of embodiements within the scope of claims 1, 29-32, 34, 35, 36, and 37.

With regard to claims 39–44, Agrawal et al. appears to teach that both 3'-end and 5'-end loops are possible (see page 8, beginning at line 33; page 17, lines 19-23; claim 14; and Fig. 7). Accordingly, different positional relationships between the target hybridizing and self-complementary regions are explicitly, implicitly, and inherently disclosed.

Accordingly, the instant claims remain rejected under this section as being anticipated by Agrawal et al.

Claim Rejections - 35 USC § 103—maintained

Claims 1, 29–37, 39–44, 49, and 50 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (WO 94/01550), as applied to the claims above, Beigelman et al. (1995) *Nucleic Acids Res.* 23:4434-4442, and Colman (1990) *J. Cell Science* 97:399-409.

Response to Arguments

Applicant's arguments filed 12/7/06 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants' arguments (page 15 of 17) with regard to Agrawal et al. have already been addressed (see Response to Arguments, above). Agrawal et al. is deficient only with regard to instant claim 33. Agrawal et al. do not explicitly teach that any of the nucleotides within the target-hybridizing portion of an oligonucleotide (i.e., the "first portion) may be modified with any of the specific moieties now recited in claim 33.

Agrawal et al., do teach, however, that the self-stabilized oligonucleotides may be rendered hyperstabilized by the incorporation of one or more 2' sugar or phosphate backbone modifications into the target hybridizing or self-complementary region of the oligo (page 16). Agrawal et al. acknowledge that limitations with regard to the number of modifications in the self-complementary region (i.e., the further portion) are not critical since the self-complementary region does not need to support RNase H1 cleavage (page 16). By this disclosure, Agrawal et al. implicitly acknowledge that the degree and/or type of modification applied to the target hybridizing region (first portion) is a result-effective variable, since the target hybridizing region must support RNase H1 cleavage. One of skill would recognize the relationship between the degree and/or type of 2' modification and the balance between RNase H1 activity and nuclease stability.

In fact, the prior art recognizes that chemical modification is a result-effective variable for both ribozymes and antisense molecules, as evidenced by both Beigelman and Colman. Further, the prior art recognizes that ribozymes and antisense molecules operate by different mechanisms, and that, therefore, chemical modification influences each type of molecule in

different relative fashions according to these mechanistic differences. Whereas antisense molecules typically operate by triggering RNase H1, ribozymes are self-contained catalysts, comprising both antisense and catalytic domains, requiring different relative considerations with regard to the placement, selection, and degree of modification used to stabilize and enhance each type of molecule. One of skill in the art would recognize these mechanistic differences, yet understand that each type of molecule is susceptible to endo- and exo-nucleolytic degradation inasmuch as each is composed of polyribonucleotides.

Accordingly, Applicants arguments that the Agrawal reference in view of the Beigelman reference and the Coleman reference do not teach incorporating 2' modifications to an oligonucleotide first portion comprising at least 6 contiguous nucleotides, and in fact, teach away from making such modifications (pages 15 and 16 of 17) is unpersuasive.

Beigelman et al. is considered to be representative of the knowledge of one of skill in the art with regard to the types of chemical modifications that may be applied to oligonucleotide-based drugs and reagents in general. At the time of invention, the prior art recognized that antisense oligonucleotides and ribozymes were alternative members of a growing collection of nucleic acid-based tools for inhibiting gene expression (see Colman). In this light, Beigelman et al. teach in general that serum nuclease degradation of nucleic-acid based drugs such as ribozymes is an important consideration for oligonucleotide stability and overall activity in vitro and in vivo. One of skill would be commended to the teachings of Beigelman et al. for guidance as to the types of modifications that may or may not be suitable for incorporation into antisense oligonucleotides, since antisense and ribozymes are art-recognized equivalents, possessing similar chemical and functional characteristics. Among other things, Beigelman et al. teach that

2'-deoxy-2'-amino and arabino modifications closely mimic the conformational and functional (e.g. hydrogen bonding) properties of natural ribonucleotides (page 4434). Beigelman et al. teach further that optimization of modifications at positions U4 and U7 by introducing 2'-arabino, 2'-NH2, 2"-C-allyl, 2'-=CH2 and 2'-=CF2 nucleotides in combination with 2'-O-Me substitutions (Rzs 3--17) gave significant increases in nuclease resistance for these ribozymes, while having variable effects on catalytic activity (page 4438). Thus, although Beigelman et al. teach that limits exist with regard to the extent of modification, Beigelman et al. teach that 2'-NH2 modifications are highly suitable, and the combined references as a whole provide ample motivation to apply each of the teachings to make and use both partially and fully modified oligonucleotides with a variety of modifications, including 2'-NH2, as taught by Beigelman, to produce self-stabilized antisense oligonucleotides, according to Agrawal et al, having maximum stability and yet optimal inhibitory activity in cells in vitro and in vivo.

Accordingly, the instant claims remain rejected under this section as being prima facie obvious over the cited prior art references.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
Examiner Art Unit 1635
January 25, 2007

SEAN McGARRY
PRIMARY EXAMINER
1635